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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,738	05/26/2000	Daniel A. Vallera	11983-004001	1069

7590 07/03/2002

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EXAMINER
SORBELLO, ELEANOR

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,738	VALLERA ET AL.	
	Examin r	Art Unit	
	Eleanor Sorbello	1632	

-- The MAILING DATE of this communication appears on th cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

Response to amendment

1. Applicant's supplemental amendment filed 4/23/02, paper number 7 with the Declaration of Daniel Vallera, and applicants amendment filed 3/25/02 as paper number 5 has been entered, and all three will be considered in this office action. Claims 17, 19 have been amended, in paper no. 7; claims 23, 38, 39 and 43 have been amended in paper no. 5; and claim 35 has been canceled. **Claims 1-34, 36-43 are pending.** Applicant's amendments and arguments have been thoroughly reviewed, and are persuasive to a point for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's argument.

2. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The communication filed on 3/21/02 is not fully responsive to the Office communication mailed 09/14/01 for the reason(s) set forth on the attached Notice to Comply With the Sequence Rules or CRF Diskette Problem Report.

Claim Rejections - 35 USC § 112

4. Claim 34 remains rejected under 35 U.S.C. 112 second paragraph, for lacking antecedent basis for the limitation, "said population of claim 20". Claim 34 has not been amended as required in office action dated 9/14/01.

5. Claims 1-34, 36-43 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling for** (1) a targeting cell comprising a retroviral vector comprising a nucleic acid sequence encoding a fusion protein comprising (a) a targeting domain comprising a cytokine such as IL3 or IL4 or GM-CSF (b) a toxic domain such as DT, DT390, PE or BAX and (2) for the treatment of myeloid leukemia or systemic leukemia by the administration of said targeting cells, **does not** reasonably provide enablement for the other limitations encompassed by the claims. Applicant's arguments have been fully considered but are only persuasive to a point.

Applicants argue the enablement rejection under two sections namely (a) and (b) in their response dated 3/25/02 page 8.

Applicants argue that all the references used by the examiner in support of her enablement rejection, indicate that for ex vivo experimentation the obstacles to gene therapy are either absent or substantially minimized. However, examiner notes that applicants claims are not limited to ex vivo therapy. The claims do not require the targeting cell to be made ex vivo or be isolated. Examiner therefore rebuts applicants arguments with regards Miller's use of carefully selected patient's cells and the production of tumor infiltrating lymphocytes which comprise potentially tumoricidal

genes, which therefore does not apply. Moreover, the claims are unduly broad as they encompass any target cell that comprises any vector encoding any targeting domain and any toxic domain. Applicants argue that even in the Deonarian reference a level of optimism abounds with regards ex vivo therapy. However, examiner argues that this methodology of administering a gene and obtaining a therapeutic response is not enabled across the board and therefore applicants are required to show support for their broad claims because the prior art does not teach one how to make and use the invention as claimed. Similarly, applicants argue about the Crystal reference and that Crystal is highly optimistic about ex vivo gene therapy, and of particular relevance to using T cells for gene delivery.

Applicants further argue the advantages of ex vivo gene therapy, and the ability to select for the relevant protein. As stated in the previous paragraph, the claims of this applicantion are not limited to ex vivo gene therapy. Further, the claims are unduly broad as explained above. Applicants go on to argue that the ex vivo methodology of this application has two "layers" of targeting that particularly enhance the chances of its success in terms of cell targeting, which examiner contends is problematic. However, examiner argues that even if the claims are directed to transfecting of targeting cells ex vivo and subsequently administering the cells that produce a requisite amount of the desired protein, the ultimate functioning is required once the cell is administered which is in vivo. The question is, will the cell reach its target and kill the desired pathogenic cell? As stated before, the claims are unduly broad, and applicants argue that one of skill in the art will know the range of cell receptors and how to search the medical

literature and use routine experimentation to decide on the suitable molecule for use as a targeting domain. As stated before, in view of the fact that the nature of this invention is not enabled across the board, it would require undue experimentation that is not exactly routine to decide on a suitable molecule as a targeting domain. The claims encompasses any cell comprising any vector encoding any toxic domain for the treatment of the broadly claimed diseases ranging from cancer to autoimmune diseases or diseases resulting from pathogenic microorganisms. Applicants further argue that with regards administration, administration of the targeting cells can be accomplished either at the site of the disease or systemically, and that the targeting cells of the instant applicantion have the ability to home to and concentrate at the disease site. Applicants argue that as described in Example 6, they have shown inhibition of tumor growth in the flanks of mice by systemic administration of the relevant targeting cells. Examiner agrees that applicants have shown this specific example for which applicants were granted scope of enablement for the treatment of myeloid leukemia wherein a retroviral vector encoding sigIL-4DT390 was administered.

In the supplemental response and declaration, applicants have supplied several references with a view to broaden the scope of the treatments enabled. Applicants argue that the reference by Bacha that teaches a model mouse for Rheumatoid Arthritis was treated efficiently with immunotoxin and DT or fragment. Applicants argue that the instant invention which is directed to treatment by administering cells, would reduce the toxicity resulting from conventional immunotoxic therapy which involves the direct administration of an immunotoxin. However, examiner argues that the claims are

directed to treatment by the administration of cells comprising a nucleic acid sequence encoding the fusion protein, comprising two elements, one of which is toxic to the cell it targets, and therefore the enablement rejection still holds because one cannot extrapolate from the results of protein therapy to that which will occur when a cell comprising a nucleic acid is administered. Similarly applicants have argued that the instant invention may be extrapolated to include the treatment of psoriasis, as in the teachings of Moreland and Martin. Here too, the immunotoxin, or protein therapy was used for treatment and not a nucleic acid encoding such. Similarly, applicants have supplied a reference by Schito who teaches the control of HIV-1 infection in a model by the administration of cytokines and DT or a fragment.

However as stated above, in view of the breadth of the claims, nature of the invention, lack of guidance in the specification, and unpredictability in the art, one of skill will require undue experimentation to make and use the invention as claimed.

6. Claims 1-34, 36-43 remain rejected as containing subject matter that was not described in the specification as to reasonably convey to one skilled in the relevant art at the time the application was filed, had possession of the claimed invention.

Applicants argue that there is no requirement to provide nucleotide sequences encoding all fusion proteins that are to be used in the constructs and targeting cells. Applicants attempt to support their argument by listing certain patents that have issued recently that do not contain such descriptions of nucleotide sequences. For instance, applicants argue that US 6,342,345 broadly claim a reporter protein component in one

embodiment of a fusion protein and a nucleic acid encoding such a fusion protein. However, examiner argues that while each case is evaluated on its own merits, the crux of the '345 patent is a reporter system comprising two protein moieties. Further, the prosecution history of this particular case is not known and will need to be reviewed to decide if there is a discrepancy. Additionally, the written description guidelines that are in use currently may not have been in use at the time of the prosecution of the '345 patent. However, the instant invention claims nucleic acid sequences that encode fusion proteins comprising a targeting domain and a toxic domain. As such, applicants claims are directed to a nucleic acids that encode proteins that have a specific function. Applicants argue that the representative polypeptides listed as being useful fusion proteins were known polypeptides. However, examiner maintains that the specification fails to describe a specific identifying structural characteristic that would tie the genus of fusion proteins having the same function as claimed in the instant invention. As stated before, the critical elements such as the linker polypeptides or the nucleotide sequences that encode them were not described in the specification. Additionally, as of the filing date of the instant application, it is unclear that fusion proteins that have the properties of binding affinity to a pathogenic cell were described.

Applicants argue that they have provided multiple examples of polypeptides useful as targeting domains and toxic domains, and that additionally even though not required applicants argue that they have provided references directing the examiner to the nucleic acids encoding such. However, examiner argues that the claimed invention is directed to a targeting cell comprising a vector encoding a fusion protein which will

bind to a pathogenic cell and not to individual independent polypeptides. Further applicants argue that linker polypeptides are not required and directed examiner to the specification. However, examiner notes that the specification states that a linker sequence may not be present but the that linker sequences may be 1-30 or even 50 amino acids long.

Applicants claim that the references provided contain the sequences of nucleic acids encoding the species as claimed in claims 5, 19 and 31 and that they are not required to describe them. However, examiner argues that applicants are thus providing references of nucleic acids taught in the prior art that encode independent polypeptides and not the fusion proteins of this invention ie. because applicants claims are directed at fusion proteins with a specific function, not its components separately. Applicants further argue that there is a direct correlation of the two domains of the fusion protein and their structures. That the toxicity of the toxic domain is a direct consequence of its amino acid sequence and thus the nucleotide encoding it, and similarly the function of the targeting domain to bind to receptors/ligands on target cells is a direct consequence of their known amino acid structures.

Therefore, as stated above, description of independent components that may together comprise a fusion protein that has a specified function, is not an adequate description for a nucleic acid encoding a fusion protein.

Therefore, as stated in previous office action, a skilled artisan cannot envision the detailed chemical structure of all of the nucleic acids encoding fusion proteins other than fusion protein sigIL-4DT390 and sigil-4PE, LNCXIL3-DT and LNCXIL-3BAX.

Claim Rejections - 35 USC § 103

7. Claims 1-33, 36-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chan, Chuang-Huang et al. (Blood, Vol. 86. No. 7, 1995, pages 2732-2740 and Blood Vol 88, No. 4 Aug. 15, 1996, pages 1445-1456) in view of Yang, An-Gang (Nature Biotechnology, Vol. 15 , 1997, pages 46-51) and further in view of Chen, Si.,-Yi.(Nature vo. 385, Jan. 1997).

Applicants argue that the Chan et al. references fail to suggest the desirability of using targeting cells of any sort to direct expression of a gene encoding an immunotoxic protein. However, examiner argues that Chan et al. actually anticipates targeting cells comprising a murine GM-CSF gene spliced to a truncated form of DT gene encoding a fusion toxin bearing the MGM-CSF receptor. (See Blood, vol. 86, page 2732, col. 2, last paragraph – paragraph. bridging col. 1 of page 2733). Chan constructed fusion toxin targeting cells bearing mGM-CSF receptor to destroy myeloid leukemic cells.

Applicants argue that Yang and Chen describe experiments wherein antibodies or antibody fragments are exclusively used as targeting domains in immunotoxins, and that the references do not include any other targeting domain other than antibodies. However, examiner argues that all the references combined teach all the required elements of the claims. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the

claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Yang and Chen teach treatment of viral infections and demonstrate the principle that mammalian cells can be genetically modified to produce targeted toxins. In the case of Yang and Chen they teach targeted antibody-toxin molecules. Examiner argues that antibodies are targeting domains wherein the antibody is the first member of the fusion protein.

Therefore, claims 1-33, 36-43 remain rejected as stated in paragraph 11 of office action dated 9/11/01 for being obvious.

Conclusion

8. Claims 1-34, 36-43 remain rejected.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

Eleanor Sorbello

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Notice to Comply	Application N. 09/579,738	Applicant(s) Vallera
	Examiner Sorbello	Art Unit 1632

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☒ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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